

April 14, 2014

Dear Dr. Naser:

Please find enclosed the edited manuscript in Word format (file name: 9605-review.doc).

Title: Phenol-based endoscopic ultrasound-guided celiac plexus neurolysis for East Asian alcohol-intolerant cancer patients: A pilot study

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved in the following ways in accordance with the suggestions of the reviewers:

1. The formatting has been updated.
2. Revisions have been made in accordance with the reviewers' suggestions.

(1) Reviewer 1

EUS guided CPN is an evolution from percutaneous CPN, with an efficacy and acceptability well documented by many meta analysis; however your study raises some queries which need to be addressed upon.

Comment 1: The study lacks the numeral standards for statistical significance.

Reply

As you pointed out, a drawback of this study was its small sample size; therefore, this trial was regarded as a pilot study. We have added sentences about the limitations of a small sample size to the Discussion section.

Comment 2: Chemoradiation has shown to influence the efficacy of CPN; none of your patients in alcoholic group, and almost all the patients in phenolic group received it: the superior results in the phenolic group could be attributed to it though.

Reply

As you pointed out, chemoradiation affects pain relief after EUS-CPN. However, chemotherapy also has the same effect, as Gunaratnam *et al.* reported that chemotherapy

and chemoradiation both decreased pain after EUS-CPN, and there were no significant differences in pain scores between patients receiving chemotherapy alone and those receiving chemoradiotherapy (*Gastrointest Endosc* 2001; 54: 316-324).

In our study, the percentages of patients treated with chemoradiotherapy were 33% and 0% in the phenol and ethanol groups, respectively; the percentages of patients treated with chemotherapy and chemoradiotherapy were 88% and 69% in the phenol and ethanol groups, respectively. There was no significant difference in adjuvant treatments between the two groups using Fisher's exact test.

Comment 3: The tables lack the arrangement and assortment with many p-values missing in conjoint groups.

Reply

We have deleted Table 3 according to advice received from the other reviewer. In Table 3 of the original manuscript, *P*-values were not included for each complication when there was no significant difference between the two groups. The *P*-values by Fisher's exact test were 0.27, 1.0, 1.0, and 1.0 for diarrhea, burning pain, inebriation, and hypotension, respectively.

Comment 4: The bias in technique of CPN, in alcoholic and phenolic group can't be nullified.

Reply

We have interpreted your comment to mean that the two techniques used were not a limitation in this study. Accordingly, we have deleted these sentences from the Discussion section.

Comment 5: The study would be better served if the patient's were randomized to different neurolytics.

Reply

We agree with your comment. However, no study has reported in detail on phenol in EUS-CPN. Therefore, we did not know the efficacy of phenol during the planning phase of this study, and thus, performed a pilot study investigating the use of phenol for patients with alcohol intolerance. Therefore, we have reported these findings as a pilot study. In the current study, we confirmed that the pain-relieving effect of phenol was comparable to that of ethanol, and had a low incidence of side effects. We are planning a future randomized, comparative study comparing ethanol and phenol.

Comment 6: Were pre-operative antibiotics used in any of the groups and if not why, and how you decided not to use any local anesthetic in phenolic group, not knowing whether it would cause immediate pain or not.

Reply

Pre-operative antibiotics:

O'Toole *et al.* reported a large case series of 189 EUS-celiac plexus block (CPB) and 31 EUS-celiac plexus neurolysis (CPN) procedures. For CPB, a mixture of 20-30 mL of bupivacaine and triamcinolone was injected. For CPN, 10 mL of bupivacaine was injected, followed by 20 mL of absolute ethanol. No patients received prophylactic antibiotics prior to the procedure. They reported that a retroperitoneal abscess occurred in 1 case after CPB. They suggested that the retroperitoneal abscess was related more to CPB and less to CPN because the alcohol had sterilized the injected area. (*Endoscopy* 2009; 41: 593-597) On the basis of these results, we have not used prophylactic antibiotics routinely prior to ethanol-based EUS-CPN.

Meanwhile, phenol was once widely used as an antiseptic; therefore, during the planning of the study we speculated that the rate of infectious complications would be extremely low, and decided against the use of antibiotics prior to phenol-based EUS-CPN.

Local anesthetic agent:

Because it has been reported that phenol has an immediate local anesthetic effect, we decided not to use any local anesthetic agent in the phenol group. We have added this point in the Methods section.

Comment 7: What were post procedural criteria for a successful CPN.

Reply

As you pointed out, our explanations of outcome parameters were unclear in the original manuscript; therefore, we have included a clearer description of the endpoints and defined them as follows.

The primary endpoint was the difference in the positive response rate between the phenol and ethanol groups on postoperative day 7.

Secondary endpoints included the time to onset of pain relief, duration of pain relief, and complication rates.

We have added this information to the revised manuscript.

Comment 8: The study needs some EUS picto-graphs; pre and post-procedural of phenolic and alcoholic groups.

Reply

In the revised manuscript, we have included a bar chart regarding pain relief on postoperative day 7, which replaces Table 2, and have included a box-plot regarding the time to onset of pain relief, which replaces Figure 1 of the original manuscript.

(2) Reviewer 2

The authors presented the use of phenol as injectate in EUS-CPN as an alternative to ethanol. The technique is original and it has not been reported previously.

Major remarks

Comment 1: The rationale for using phenol has been found in alcohol intolerance among Asian population. I would suggest to emphasize this aspect in the title.

Reply

Thank you for your comment. We agree with your assertion and have changed the title in accordance with your suggestion.

Comment 2: The main limitation is represented by the small number of patients. Thus I suggest to call this article "pilot study". As a consequence I would recommend to change the title as follows: Phenol-based endoscopic ultrasound-guided celiac plexus neurolysis for east-Asian alcohol-intolerant cancer patients: a pilot study.

Reply

We have added some sentences about the small sample size to the revised manuscript, and have changed the title in accordance with your comment.

Minor remarks

Comment 1: Table 2 and 3 are not needed as they replicate data reported in the text

Reply

We have deleted **Tables 2 and 3** in accordance with your advice.

3. The references and typesetting have been corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, reading "Hirotochi Ishiwatari". The script is cursive and fluid, with the first name "Hirotochi" and last name "Ishiwatari" clearly distinguishable.

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